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Title of Thesis: "Possible Triggers and Temporal Patterns of Implantable Cardioverter
Defibrillator Discharges: A Preliminary Study"

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A handwritten signature in black ink, appearing to read 'Dana L. Tucker', with a stylized flourish at the end.

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ABSTRACT

Title of Thesis: Possible Triggers and Temporal Patterns of Implantable Cardioverter Defibrillator Discharges: A Preliminary Study

Dana L. Tucker, Master of Science, 1999

Thesis directed by: David S. Krantz, Ph.D.,
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The present study investigated: (1) mental and physical activities as possible triggers of implantable cardioverter defibrillator discharges; and (2) the temporal patterns of those discharges in order to provide the rationale for a larger-scale study.

Retrospective interviews of patients with coronary artery disease and implantable cardioverter defibrillators were conducted to determine frequency of discharges and timing of discharges as well as specific circumstances surrounding those discharges. The interview also collected information regarding the usual activity levels of the patients to serve as control or baseline data. The case-crossover method was used to approach the data of 32 patients who were interviewed. Over a two-year period, 20 of the 32 patients had experienced discharges. Elevated Mantel-Haenszel estimates of relative risk were found for high physical exertion, sexual activity, high mental activity, tension or stress, and anger, but these elevated risks were statistically non-significant given this small sample size. Chi-square analysis of a circadian pattern of discharges was statistically non-significant, but there was evidence of a seasonal variation in number of discharges ($\chi^2 = 9.00$, $p = 0.029$). This seasonal pattern revealed a peak prevalence of incidents during the winter months and a smaller peak during summer months.

Possible Triggers and Temporal Patterns
of Implantable Cardioverter Defibrillator Discharges:
A Preliminary Study

by

Dana L. Tucker

Master's Thesis submitted to the Faculty of the Department of Medical and Clinical
Psychology Graduate Program of the Uniformed Services University
of the Health Sciences in partial fulfillment of the requirements
for the degree of Master of Science, 1999

Dedication

This thesis is dedicated to Sarah Smith. Sarah might well have been working on her dissertation at this point had her life not ended tragically at the conclusion of our first year as Medical Psychology graduate students. My friend's passion for her work and her enormous capacity for caring about those around her, remarkable to me during our few months together, have been more notable to me in their absence. The thesis that follows, while perhaps not earth-shattering, would no doubt have found her to be an appreciative audience.

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INTRODUCTION

Sudden cardiac death (SCD), unexpected death occurring within 1 hour after the onset of signs and symptoms resulting from cardiac causes, is responsible for between 300,000 and 400,000 deaths per year in the United States (Hurwitz & Josephson, 1992). SCD often occurs in patients with coronary artery disease, which may be manifest by prior myocardial infarction (MI), ischemia, or left ventricular dysfunction. In some cases however, SCD may be the initial manifestation of coronary artery disease. Researchers have studied the interplay of structure and function in identifying the pathogenesis of sudden cardiac death in coronary heart disease patients, as these patients are identified to be at high risk of SCD (Bayés de Luna, Guindo, & Vinolas, 1992).

Research has focused on the acute triggers of sudden cardiac death from both the physiological (Pozzati, Pancaldi, Di Pasquale, Pinelli, & Bugiardini, 1996) and the epidemiological perspectives (Mittleman & Siscovick, 1996; Lecomte, Fornes, & Nicolas, 1996; Leor & Kloner, 1996; Leor, Poole, & Kloner, 1996). Identifying antecedents of SCD in epidemiological studies is a difficult task ("dead men tell no tales"), and has prompted use of novel methodologies to study possible triggers (Maclure, 1991; Mittleman, Maclure, & Robins, 1995; Willich, Maclure, Mittleman, Arntz, & Muller, 1993). Among the epidemiological studies, there has also developed a literature regarding the timing of SCD death, most notably that of a circadian variation (reviewed by Peters, 1996).

One development which has enhanced the study of triggers of sudden cardiac death is the success of implantable cardioverter defibrillators (ICDs) in preventing sudden

cardiac death (The Antiarrhythmics versus Implantable Defibrillators [AVID] Investigators, 1997). These devices are used to detect sustained ventricular tachyarrhythmias and convert the abnormal rhythms to normal pacing through a tiered therapy, the final step being delivery of a defibrillatory shock.

Ventricular tachycardia (VT) is defined as an abnormally rapid ventricular rhythm with aberrant ventricular excitation, is usually in excess of 150 per minute, generated within the ventricle, and is most commonly associated with electrical dissociation of the ventricle from the atrium. Sustained VT often degenerates into ventricular fibrillation (VF), an arrhythmia characterized by rapid desynchronized contraction of the ventricular muscle due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricle. The defibrillatory shock delivered by ICDs is intended to clear the chaotic wavefronts associated with fibrillation and allow the heart to restart in a normal rhythm. The circumstances surrounding discharge of an ICD are interpreted generally as analogous to sudden cardiac death, as sudden cardiac death would likely be the result of the tachyarrhythmia (which elicits ICD discharge) were no ICD therapy applied. By following patients with ICDs, researchers can more precisely define the cascade of events culminating in a defibrillatory discharge.

Studies have generally noted a circadian pattern in device therapy similar to that described in studies of sudden cardiac death (Behrens et al., 1995; Tofler et al., 1995), but there is relatively little information on specific activities acting as triggers of ICD discharge. Researchers have likewise begun to study the psychological sequelae of device implantation and discharge (Burgess, Quigley, Moran, Sutton, & Goodman, 1997). The present study was designed as a pilot project to gather information on mental and

physical activities acting as triggers of ICD discharge and information concerning timing of those discharges.

Pathogenesis of sudden cardiac death

It is believed that most episodes of SCD occur in patients with ventricular dysfunction related to a prior myocardial infarction, in which the necrotic heart muscle prevents normal transmission of electrical wavefronts. A malignant arrhythmia typically is a ventricular tachycardia, which often degenerates into ventricular fibrillation. SCD does not appear to be consistently associated with acute infarction, and there are conflicting reports of the role of significant ischemia as an immediate trigger of SCD (Margolis et al., 1975; Rapaport, 1988; Kempf & Josephson, 1984; Bayés de Luna et al., 1985; Bayés de Luna, Coumel, & Leclerc, 1989; Gomes et al., 1989; Pepine, Gottlieb, & Morganroth, 1991). What is less clear is how coronary artery disease (CAD) might cause malignant arrhythmias. Functional changes in coronary lesions, ischemia (an imbalance between supply and demand of blood, in this case to cardiac tissues), vasospastic angina (Prinzmetal's angina- chest pain attributed to spasms in coronary vasculature), and enhanced vasoreactivity in a lesioned area have been presented as potentially causing SCD by eliciting electrical instabilities in the heart leading to malignant arrhythmias (Bayés de Luna et al., 1992; Hjemdahl-Monsen, Lewis, Cairns, Chesebro, & Fuster, 1986; Hammon & Oates, 1986; Corrado, Thiene, Buja, Pantaleoni, & Maiolino, 1990). Focusing on ischemia, there is a 30% to 50% incidence of myocardial ischemia just prior to sudden cardiac death in studies reported by some of these researchers (Bayés de Luna et al., 1985; Bayés de Luna, Coumel, et al., 1989; Gomes et al., 1989; Pepine et al.,

1991). Thrombosis due to plaque fissuring and increased platelet activation and aggregation following endothelial damage have also been presented as precursors to malignant arrhythmias through eliciting ischemia (Hjemdahl-Monsen et al., 1986; Hammon and Oates, 1986).

Importance of Left Ventricular dysfunction and ischemia

The interplay of left ventricular dysfunction, electrical instability, and ischemia has been represented graphically (Figure 1), suggesting that each of the three factors influences each other, and the status of these three factors can be assessed to determine the risk for SCD in CAD patients (Bayés de Luna et al., 1992). Bayés de Luna and colleagues further described the bi-directional and direct aspects of the interaction between electrical instability and ischemia, with ischemia inducing electrical instability by slowing of conduction, changes in refractoriness (when the tissue is able to contract), and refractoriness dispersion allowing reentry.

A further distinction made by Bayés de Luna and colleagues is among types of ischemia and in the likelihood of their ability to produce SCD directly or indirectly. The types presented are severe transmural and persistent ischemia (transmural in that the ischemia is manifest across the heart tissues- endocardium, myocardium, epicardium), severe transmural and transient ischemia, and subendocardial ischemia (a minor ischemia not crossing into the myocardium). In describing severe transmural and persistent ischemia, they present evidence that this type of ischemia is most likely to directly produce SCD relative to the other types of ischemia, those of severe, transmural and transient ischemia, and subendocardial ischemia (Bayés de Luna et al., 1992). Severe

transmural and persistent ischemia is the type of ischemia which elicits myocardial infarction, and most often elicits angina. It is noted however, that direct triggering by this type of ischemia often is manifest as bradyarrhythmia, which is less frequently a cause of SCD than are VT and VF (Bayés de Luna, Guindo, & Rivera, 1989). Evidence from study of SCD in the Framingham Study suggests that while silent ischemia directly triggers SCD in cases of silent myocardial infarction, this represents a small percentage of all sudden cardiac deaths, because silent MI represents only 20% of all infarctions, and SCD appears in only about 20% of acute infarctions (Kannel & Abbot, 1984; Kannel, 1986; Kannel, Cupples, & D'Agostino, 1987).

In recalling the triangle of risk markers for sudden death (Figure 1), however, Bayés de Luna and others suggest that the indirect role of ischemia in eliciting sudden death is actually more important in most cases than are the direct influences. In that triangle, left ventricular dysfunction may influence or mediate the effect of ischemia on existing electrical instabilities in the heart. An example of this indirect influence of ischemia in eliciting sudden cardiac death would be ischemia in a region adjacent to scarring from an old myocardial infarction leading to sustained ventricular tachycardia. In support of this concept, these researchers refer to the epidemiologic evidence of ischemic heart disease incidence rates in cases of sudden cardiac death (80% to 90%), and studies in which sudden cardiac death cases were shown prospectively to have electrophysiological evidence of ischemia (Goldstein, 1994; Sharma, Asinger, Francis, Hodges, & Wyeth, 1987). They also cited a study in which patients were found retrospectively (in autopsy study) to have evidence of luminal narrowing in the four major coronary arteries (left main, left anterior descending, left circumflex and right) suggestive

of ischemia (half of those patients were known ischemic; Warnes & Roberts, 1984). To summarize, these researchers present both direct and indirect roles of ischemia in triggering SCD, and suggest that ischemia more often plays an indirect role in triggering SCD than a direct role such as that seen in severe persistent transmural ischemia.

The multifactorial problem of sudden cardiac death has been presented as a combination of vulnerable myocardium dealing with specific triggers leading to the malignant ventricular arrhythmias resulting in sudden cardiac death. Figure 2 represents this problem diagrammatically. Physical activity and mental activity have been presented as acute triggers of various cardiac events, and a review of the relevant literature will be presented at this point.

Triggers of sudden cardiac death and other cardiac events

Mental activity and physical activity have been presented as triggers for myocardial ischemia and infarction and also as possible triggers for sudden cardiac death (Mittleman et al., 1993; Mittleman, Maclure, Sherwood, et al., 1995; Krantz, Hedges, Gabbay, Klein, Falconer, Merz, Gottdiener, Lutz, & Rozanski, 1994; Blumenthal et al., 1995; Gabbay et al., 1996). Evidence for triggers of cardiac events has been presented in epidemiologic studies as well as human and animal laboratory stress studies.

In an epidemiologic study of triggering related to a natural disaster, the Northridge, California earthquake in 1994 was followed by a 35% increase in the number of admissions for myocardial infarction to coronary care units in the area (Leor & Kloner, 1996). A similar finding was presented related to Iraqi missile attacks on Israel during the 1991 Gulf War, which resulted in increased numbers of cardiac events around Tel

Aviv (Meisel et al., 1991). Cases of acute MI treated in a Tel Aviv medical center were elevated during the week following the missile attacks and data from a mobile intensive care ambulance indicated an increase in the sudden death rate during that month compared to the same month the year before.

In another epidemiologic study, Tofler and colleagues presented data that among 849 patients with acute MI, 48% reported one or more possible triggers, the most common being emotional upset (Tofler et al., 1990). Behar and colleagues presented data that identified possible external triggers in 10% of acute MI patients, but suggested that the lower percentage of possible triggers reported in their study may be due to different methods of data collection (Behar et al., 1993). They required a possible trigger to be either an uncommon emotional stress or an extraordinary physical activity.

Leor and colleagues (Leor et al., 1996) further studied the triggering of sudden cardiac death in the same Northridge earthquake cited earlier. In review of coroner reports in Los Angeles County, they found a sharp increase in the number of sudden deaths from cardiac causes. The week prior to the earthquake, the daily average of sudden deaths was 4.6 ± 2.1 , whereas there were 24 sudden cardiac deaths the day of the earthquake. Further, during the six days after the earthquake, the number of sudden deaths declined to an average of 2.7 ± 1.2 per day. Meisel and colleagues also reported on sudden death events among Israelis during the Gulf War (Weisenberg, Meisel, & David, 1996). While a rise in the incidence of SCD during the first ten days of the war was found compared to five control periods, this change did not reach statistical significance.

The Case-crossover Methodology

Mittleman and colleagues used a novel epidemiological approach, the case-crossover design, to determine the possible role of triggers in cardiac events (Mittleman et al., 1993; Mittleman, Maclure, Sherwood, et al., 1995). The case-crossover design compares each patient's pre-event activities to his or her usual levels of activities to assess the proximal physical and mental triggers of onset of the event (i.e. MI). Statistical analysis of the design has been done with the Mantel-Haenszel estimator of the relative risk (RR_{MH}), and a corresponding estimator of the variance of its logarithm, shown by Greenland and Robins (1985) to be unbiased for sparse person-time data. The RR_{MH} is comprised of a numerator, the "nonhazard" person-time of the subjects experiencing an event during the effect period after the hypothesized trigger, and a denominator, the "hazard" person-time of the subjects not experiencing an event during the effect period of the hypothesized trigger (Maclure, 1991). Interviews with 1228 patients conducted an average of four days after MI indicated that 54 (4.4%) of the patients had engaged in heavy physical exertion in the hour before onset of myocardial infarction. In the analysis employing the usual annual frequency of heavy exertion as the control value, the estimate of relative risk of MI following heavy physical exertion was 5.9 (95% CI: 4.6 to 7.7). An analysis using the frequency of heavy exertion during the control period on the day before onset as the reference value found a similar relative risk, with a wider confidence interval ($RR=5.6$, 95% CI: 2.7 to 12.8). When taking into consideration the usual levels of exercise of individual patients, the researchers found that increasing levels of physical activity were associated with progressively lower relative risks. These findings are

supported by their later reported findings related to sexual activity as a trigger of MI, in which regular physical exertion is presented as lowering risk of triggering MI by sexual activity (Muller, Mittleman, Maclure, Sherwood, & Tofler, 1996).

Regarding mental activity as a trigger, interviews with 1623 patients indicated that 39 (2.4%) of the patients reported episodes of anger within the 2 hours prior to the onset of MI (Mittleman et al., 1993; Mittleman, Maclure, Sherwood et al., 1995). The estimate of relative risk of MI following anger episodes was 2.3 (95% CI: 1.7 to 3.2). The relative risk associated with anger episodes was significantly lower among regular users of aspirin, and there were nonsignificant trends towards a lower relative risk of MI following anger for women versus men, and lower risk for regular users of beta-adrenergic medications than nonusers.

The case-crossover methodology, while more sophisticated than the methodology used in some of the epidemiological studies cited earlier, does not entirely escape the biases related to retrospective reporting. It is possible that the patients' awareness of their myocardial infarction affected their retrospective reporting of physical or mental activities (Maclure, 1991; Mittleman, Maclure, & Robins, 1995; Marshall & Jackson, 1993; Greenland, 1996). These researchers and others have begun to investigate the role of physical and mental activities as acute triggers of cardiovascular events using prospective measures to avoid the biases inherent in the retrospective studies discussed here.

Laboratory studies and prognosis

The epidemiological studies just discussed are correlational in nature, and thus cannot be used to determine causal relationships between mental stressors and cardiac

events. Laboratory studies of mental stress as a trigger of cardiac events implement a more experimental paradigm to explore possible causal relationships. These studies have shown that laboratory mental stressors can elicit ischemia in a substantial subset of patients with coronary artery disease (see Krantz, Kop, Santiago, & Gottdiener, 1996, for review). The ischemia induced is typically silent, is infrequently accompanied by electrocardiographic evidences of ischemia, and occurs primarily among patients with evidence of exercise-inducible ischemia.

Ischemia with exercise testing is well established as a predictor of poor prognosis, and daily life ischemia has been shown to be an indicator of worse prognosis compared to those who do not manifest daily life ischemia (Deedwania & Carbajal, 1990; Rocco et al., 1987). Jain, Burg, Soufer, and Zaret (1995) reported that at 2-year follow-up, 10 of 15 patients with mental stress-induced LV dysfunction (ejection fraction decreases $> 5\%$) had adverse events compared to only 4 of 15 with no mental stress-induced LV dysfunction. Cautions to overstating the importance of this study include the low number of subjects involved in the study, and the low number of documented myocardial infarctions (4) as opposed to the 6 events classified as unstable angina. Two more studies strengthening these findings include those of Jiang et al. (1995) and Santiago et al. (1996). Jiang et al. (1995) prospectively followed 126 patients with stable angina who underwent exercise testing and mental stress-testing using radionuclide ventriculography over an average follow-up of 3.2 years. An increased risk of clinical events (angioplasty, coronary artery bypass grafting, MI, or cardiac death; odds ratio = 2.93, $P < 0.03$) was found for patients testing positive for mental stress ischemia (defined as a transient decrease in ejection fraction of greater than 5%). Santiago and colleagues (1996)

followed up 79 patients with recent positive exercise stress tests who had also been assessed previously for mental stress-induced wall motion abnormalities with multiple stressors. Again, higher rates of new cardiac events were found in patients with mental-stress ischemia compared to patients without mental stress ischemia, but the resulting relative risk of 2.2 did not reach levels of statistical significance in the relatively small sample size.

Krantz, Kop, Santiago, et al. (1996) comment on possible mediators of the relationship between inducible mental stress-induced ischemia and prognosis. First, they point out the need to validate the findings presented earlier on the predictive value of laboratory mental stress-induced ischemia by studies in larger and more diverse patient populations. One of the four possibilities these researchers present regarding mental stress-induced ischemia and prognosis is that mental stress ischemia patients are at increased risk due to the presence of more ischemia during daily life, based on the association between mental stress ischemia and ambulatory ischemia. Another is that mental stress testing may be uncovering more severe disease in a way that supplements conventional exercise stress testing, as the mental stress ischemia is more likely in these patients. A third possibility presented by these researchers is that mental stress testing may be identifying a subset of patients with a greater susceptibility to mental stress triggers of clinical events during daily life. Lastly, they suggest that mental stress testing more closely approximates the myocardial supply and demand conditions of daily life.

Mental stress has also been presented as important in the elicitation of ventricular arrhythmias in humans and in animal models. Reich, De Silva, Lown, & Murawski (1981) studied the role of affective state in inducing arrhythmia in 117 patients with

recurrent malignant arrhythmias. They identified a psychological trigger in 21% (25) of these patients. Seventeen (68%) of these psychological triggers were anger episodes. There was no data collected regarding control periods, however, and relative risks could not therefore be assessed. In a prospective study of the relationship between psychological distress and ventricular ectopy, Follick and colleagues (1988) reported that among the 59 of 125 post-MI patients equipped with a transtelephonic ECG monitor, there was a direct relationship between self-reported distress levels and occurrence of ectopic beats. These researchers later reported a negative finding in the Cardiac Arrhythmia Pilot Study (CAPS; Follick et al., 1990). They found that biobehavioral factors were not associated with ventricular premature complexes (VPCs), nor did they predict response to antiarrhythmic therapy.

In focusing on animal models of stress-induced arrhythmia, Verrier reports that provocation of an angerlike state in dogs has been shown to decrease the vulnerable period threshold (for fibrillation) by 40% to 50% (Verrier, 1987). He further points out that the period immediately post-stress can also be particularly hazardous (for an extensive review of effects of anger on heart rhythm in patients with coronary heart disease, see Verrier & Mittleman, 1996). Verrier points to a number of studies, both animal models and human, in his assertion that the neural influences related to emotion and psychological states which induce vulnerability to arrhythmia can be posited primarily on sympathetic discharge. The hypothalamus serves as the cardinal site for neural integration of psychological processes into the central nervous system and stimulation of this structure has long been known to induce ventricular tachyarrhythmias (Hockman, Mauck, & Hoff, 1966). Satinsky, Kosowsky, & Lown (1971) presented that

stimulation of the hypothalamus increased by 10-fold the incidence of VF elicited experimentally by occlusion of the coronary artery. Further research is reviewed by Verrier that discusses the antifibrillatory influences of vagus nerve activation that acts to counterbalance the effects of sympathetic activation (Verrier & Mittleman, 1996).

Triggers of cardiac events have been studied in epidemiological studies and laboratory studies of both humans and animals. Another approach to be discussed is the literature that exists on the chronobiology of cardiac events. Time patterns for myocardial infarctions, ischemia and sudden cardiac death have been studied in an attempt to more fully understand the circumstances that lead up to cardiac events and perhaps increase the risk for those events.

The chronobiology of sudden cardiac death and other cardiac events

Sudden cardiac death and other cardiac events were at one time thought to be random events, but research into time patterns of sudden cardiac death and cardiac events in general often has revealed circadian and seasonal patterns as well as triggers. Rocco and colleagues reported in 1987 that there was a circadian rhythm for transient myocardial ischemia out of hospital, with the greatest density of ischemic time occurring between 6:00 AM and noon (Rocco et al., 1987). Mulcahy and colleagues also found a circadian variation in total ischemic burden, with a morning peak and a smaller evening peak (Mulcahy et al., 1988). These researchers demonstrated that this variation was abolished by use of atenolol, a beta-blocker, while the circadian pattern was not altered by nifedipine, a calcium channel blocker. More recently Krantz and colleagues (Krantz, Kop, Gabbay, et al., 1996) have confirmed the circadian rhythm in the case of ischemia,

with a morning peak and a smaller evening peak. They point out that exogenous factors such as mental and physical activities are most potent as triggers of ischemia during the morning hours, and that postural changes after awakening also contributes to the increased ischemia in the morning. They suggested there is evidence for an endogenous, activity-independent circadian influence on ischemic susceptibility that is both independent of those exogenous factors and sustains the increase in ischemia upon awakening.

Studies of strokes and acute myocardial infarction have also pointed out a circadian pattern to their incidences, with a morning peak being found consistently across studies. Muller and colleagues reported as early as 1985 on the circadian pattern of acute myocardial infarction, noting the morning peak in a study of almost 3,000 patients with MI (Muller et al., 1985). They commented that the pattern was not discernible among patients using beta-blockers, positing the failure to discern the pattern to two possible explanations: a lack of statistical power, or the possibility that the medications blunt the increased myocardial demand for oxygen that occurs in the morning and modify other catecholamine-related changes. The explanation regarding blunted myocardial oxygen demand hints at the roles mental and physical activity might play. Marler and colleagues studied the morning increase in onset of ischemic stroke and found that in a sample of over 1,000 patients there was a peak from 10:00 AM to noon (Marler et al., 1989). The rate of incidence of stroke decreased consistently until a nadir just before midnight.

Studies of circadian variation in sudden cardiac death also exhibit this morning peak in onset of events. Willich and colleagues studied the incidence of sudden cardiac death in the Framingham cohort and found that among the 5,209 persons in the cohort

there was a statistically significant peak incidence from 7 to 9 AM in the cases of sudden cardiac death ($n=429$; Willich et al., 1987). They reported that risk of sudden cardiac death was at least 70% higher during the peak period than was the average risk during other times of the day. In another study by the same group, a similar circadian pattern was revealed in incidence of sudden cardiac death with a peak from 9:00 A.M. to 12:00 noon (Willich, Goldberg, Maclure, Perriello, & Muller, 1992). An analysis of time of death adjusted for individual wake-times of the 94 decedents demonstrated an increased onset of sudden cardiac death during the initial 3-hour interval after awakening with a relative risk of 2.6 (95% confidence interval= 1.6, 4.2).

Mittleman and colleagues have continued to examine the circadian patterns of acute cardiovascular events and recently presented a meta-analysis of 30 reports on acute MI and 19 studies on sudden cardiac death (Cohen, Rohtla, Lavery, Muller, & Mittleman, 1997). They noted that the patterns for both MI and SCD were strikingly similar. Figures 3 and 4 present the incidence rates over the time of day for infarctions and sudden cardiac deaths respectively from the Cohen and colleagues' meta-analysis (1997). While the authors focus on the statistically higher incidence rate for infarction and sudden cardiac deaths, it may also be noted that at least for sudden cardiac deaths, the number of deaths during the 0:00 to 5:59 time period is likely significantly lower. That rates are lower during that time period, a time period of relative inactivity, further supports hypotheses regarding the importance of mental and physical activities in triggering cardiac events.

Seasonal patterns for cardiac events have been reported, with events occurring more frequently during the winter months compared with other seasons (Beard, Fuster, & Elveback, 1982; Ornato, Siegel, Craren, & Nelson, 1990; Pasqualetti, Colantonio, Casale,

Acitelli, & Natali, 1990; Douglas, al-Sayer, Rawles, & Allan, 1991; Nicolau, Haus, Popescu, Sackett-Lundeen, & Petrescu, 1991; Kloner, Poole, & Perritt, 1998). Kloner and colleagues, reporting on over 220,000 cases of deaths due to ischemic and atherosclerotic heart disease in Los Angeles County over 12 years, noted significantly higher rates during the months of December and January. Noting that in this region the climate is relatively mild, the researchers hypothesized possible mechanisms of changes in diet during holidays (sodium, alcohol, general increased caloric intake), stress during the holidays, and increased respiratory infections during that time of year (Kloner et al., 1998). Beard, Fuster and Elveback presented the finding that in Rochester, Minnesota, from 1950 to 1975, sudden cardiac death occurred more frequently in winter, but that this difference was not statistically significant (Beard et al., 1982). Pasqualetti and colleagues reported that in 269 cases of sudden cardiac death occurring between 1970 and 1987, these deaths occurred more frequently during the months from October to January (Pasqualetti et al., 1990). Some of the researchers hypothesize temperature extremes play a major role, while others such as Kloner focus more on behavioral factors such as diet and stress. A possibility not addressed by these numerous researchers is the effect from seasonal affective disorders. Recently, attention has turned towards the use of implantable cardioverter defibrillators, which have been used in patients with malignant arrhythmias. Fries and colleagues reported a peak of tachyarrhythmic events recorded in implantable cardioverter defibrillators in patients during very cold and very hot periods of the year (Fries, Heisel, Jung, & Schieffer, 1997). A more thorough explanation of implantable cardioverter defibrillators follows.

Implantable cardioverter defibrillators

Implantable cardioverter-defibrillators (ICDs) have been used to treat patients with lifethreatening ventricular arrhythmias since 1980 (Mirowski et al., 1980). The ICD is an electronic device which consists of a generator and a lead system (for a clinical overview of ICD technology, efficacy, indications, and evaluation of delivered therapy, see Groh, Foreman, & Zipes, 1998). The purpose of the device is to monitor heart rhythm and treat detected abnormal heart rhythms using variable modalities. Current ICDs may include the capacity to provide pacing to treat bradyarrhythmias, competitive pacing or synchronized cardioversion to treat sustained VT, and debrillatory shocks to treat VF. Cardioversion delivers a synchronized high-voltage discharge to depolarize a sufficient mass of the myocardium to stop the ventricular tachycardia. Current implantable cardioverter defibrillators also store information about the arrhythmias. This information can be used to determine the type of therapy delivered, the type of arrhythmia eliciting the therapy, and the heart's response to that therapy. The stored information also allows more precise analysis of timing factors, which allows further investigation into the circumstances just prior to therapy, and patterns of discharge over time.

Study of an ICD patient population with known coronary artery disease (CAD) allows more efficient analyses of aspects of sudden cardiac death, including temporal patterns and acute triggers such as mental and physical activity. Because 80% to 90% of sudden cardiac deaths occur in patients with coronary artery disease (Goldstein, 1994), study of a patient population with the combination of CAD and known risk for malignant arrhythmias provides an efficient model for SCD. Another aspect of the efficiency in the

model is that one patient may provide reports on multiple discharge events, each representing potential sudden death events.

Studies on circadian and seasonal patterns of ICD discharges

Researchers have thus begun to study the use of ICDs, and to compare those findings with findings related to cardiac events, most notably sudden cardiac death. Circadian patterns have been one of the targets of study. In the last five years at least seven studies have been conducted regarding the time patterns of implantable cardioverter defibrillator discharges (Lampert, Rosenfeld, Batsford, Lee, & McPherson, 1994; d'Avila, Wellens, Andries, & Brugada, 1995; Wood et al., 1995; Behrens et al., 1995; Tofler et al., 1995; Mallavarapu et al., 1995). The composite of these studies indicates the familiar higher rate of incidence in the morning hours holds true with the end point in question.

For example, Behrens and colleagues studied 78 consecutive ICD patients in Berlin, Germany (Behrens et al., 1995). During a mean follow-up period of 18 months, 39 (50%) of the patients had 207 shock episodes terminating VT that could be related to an exact time of onset. They found a primary morning peak between 7:00 AM and 11:00 AM and a secondary, much smaller peak between 4:00 PM and 8:00 PM.

Tofler and his associates also noted a higher proportion of VT occurring in the late morning compared to other times of day (Tofler et al., 1995). In this study the researchers differentiated between rapid and less rapid ventricular arrhythmias ($>$ or $<$ 250 beats per minute), and found the pattern held in both categories. The only exception to the pattern was in the subgroup of patients with ejection fraction $<20\%$ at the time of implantation, the distribution of less rapid ventricular arrhythmias was uniform over 24

hours (1087 of 8449, or 13% of all less rapid VT episodes). The researchers hypothesized that in some patients faster unstable ventricular tachycardic episodes may have different precipitants than do slower, potentially more stable VT episodes, but present that the hypothesis needs further exploration. Again, at least one study has indicated a seasonal variation in arrhythmias sensed by implantable defibrillators. These researchers explained that finding with the Klima Michel Model which suggests that the increased frequency of tachyarrhythmic events during winter months is tied to thermal extremes and the stress those extremes place on the body (Fries et al., 1997).

Study rationale and hypotheses

Researchers are in the initial stages of addressing the question of whether there are specific physical and mental activities that act as triggers of discharge events. Further, while research suggests a circadian pattern and possibly a seasonal variation to discharge events in patients with coronary artery disease and ICDs, the reason for this pattern is not clear. Some of the possible explanations for the circadian patterns have included physiological responses to the change in posture related to awakening, and responses to physical and mental activity, to include heightened sympathetic activity and/or a reduction in vagal tone. The possible explanations for seasonal patterns of discharge have included thermal extremes (Fries et al., 1997) and more recent hypothesized explanations have included excess sodium and caloric intake and stress during the holiday season, as well as increased rates of colds and respiratory infections (Kloner et al., 1998). Further, it may be that affective states such as seasonal affective disorder are influencing temporal patterns of discharge. A technical explanation might include the temporal

patterns of device implantation. This pilot study is an initial attempt to address the possible role of physical and mental activities as triggers of defibrillator discharge. The primary study hypothesis is that: (1) both physical and mental activities increase risk for defibrillator discharges in patients with coronary artery disease and implantable cardioverter defibrillators. (2) It is further hypothesized that there will be a temporal pattern of arrhythmias with an increase of discharges occurring in the morning (6:00 AM to 12:00 AM), which would confirm the temporal pattern of arrhythmias noted in other studies. (3) A third hypothesis related to temporal patterns is that there is a seasonal pattern of discharges, with a greater incidence during the winter months. Another general aim of the study is to quantify discharge rates in a sample similar to that for a planned prospective study of triggers of arrhythmia in defibrillator patients.

METHODS

Subjects

Subjects were drawn from a database of patients followed at an ICD tracking station at the Washington D.C. VA Medical Center. The database detailed implant etiology (general cardiac conditions possibly predisposing to arrhythmia) and indication of pace (the specific type of arrhythmia to which the patient was vulnerable). Those who had indications of cardiovascular disease as presented by implant etiology were contacted and asked to participate in the telephone interview (see Table 1; Patient 26 had indications of CAD in other records). Thirty-two patients were reached by phone and provided baseline and where applicable, discharge information on up to two discharge events in the past 2 years. Further data was gathered from electronic files kept at the VA Medical Center when such data was available, as not all patients' care is followed at that center. Table 2 presents further demographic data. The mean age of patients was 67.07 ± 9.61 .

Regarding a measure of left ventricular dysfunction, the mean left ventricular ejection fraction of the 13 patients for whom records were available was $35.08\% \pm 12.87\%$.

Twelve (38%) of the patients reported having undergone a coronary artery bypass graft (CABG) procedure, and 5 (16%) of the patients reported having undergone an angioplasty (PTCA) procedure. A further indication of cardiac condition, history of myocardial infarction, was noted for 29 (91%) of the patients, and 2 of those patients (6%) had also undergone both CABG and PTCA. Nine (28%) of the patients were diabetic, and the mean body mass index (BMI) was 27.29 ± 6.07 (guidelines recently published by the National Heart, Lung, and Blood Institute indicate that a BMI of 25 to 29.9 is considered

overweight, and 30 or above is considered obese and at greatly increased risk for poor health outcomes).

Interview

The interview was an adaptation of a questionnaire developed at Deaconess Hospital for use in a planned epidemiological study of arrhythmia triggers (the TOVA study protocol; Tofler, 1995). The interview obtained information on: 1) general health history and medication information; 2) time and date of the events; and 3) the mental and physical activities just prior to those events. It further inquired as to usual activity levels and the patients' activities during the entire week prior to discharge (see Appendix A). Activities assessed included high physical exertion, sex, anger, tension or stress, high mental activity, smoking, being cold or shivering, being hot or sweating, taking over-the-counter medications, other drug use, and eating. Responses to the questionnaire were noted on interview sheets as well as audiotaped to assure accurate recording of responses.

Study Design

The case-crossover design utilized by Mittleman et al. (Maclure, 1991; Mittleman et al., 1993; Mittleman, Maclure, Sherwood, et al., 1995) was used in this study. This approach was developed to assess the change in the risk of an acute event during a brief "hazard period" after exposure to a transient risk factor. With this method, each patient's activities serve as his or her control information. A one-hour hazard period immediately before the onset of a ventricular tachyarrhythmia resulting in defibrillator discharge was compared with the patient's reported usual frequency of the various types of activity.

Another control period measure was their actual level of exertion at the same time of day earlier in the week prior to the discharge.

Statistical Analysis

To test the primary hypothesis, that physical and mental activities are associated with an increased risk for defibrillator discharge, the case-crossover method was used. In the case-crossover analysis, the stratifying variable is the individual patient as in a crossover experiment. The ratio of the observed frequency of the various types of activity during the hazard period to the expected frequency (from the information on the control period) was used to calculate estimates of the relative risk using the Mantel-Haenszel method (Machauer, 1991). The primary analysis was done using the control period of “usual frequency of activity” reported by the patients. The amount of person-time spent in the activities (exposures) was estimated by multiplying the reported usual weekly frequency of the activity by an estimated duration. Unexposed person-time (person-time not spent in the activity) was then calculated by subtracting the exposed person-time in hours from the number of hours in a 2 year period. The calculated relative risk refers to the risk of having a defibrillator discharge during a period during or just following an activity as compared with the risk during non-activity periods. As this was a pilot study, a power analysis was not conducted prior to investigation, however issues of sample size and power will be considered in the discussion.

To test the hypotheses regarding circadian and seasonal patterns, Chi square analyses of the pooled events were utilized. The circadian pattern analysis compared the number of defibrillator discharges occurring during four time periods (12:00 AM to 6:00

AM, 6:00 AM to 12:00 PM, 12:00 PM to 6:00 PM, and 6:00 PM to 12:00 AM). The seasonal pattern analysis in a similar manner compared the number of defibrillator discharges occurring during the four seasons (Winter, Spring, Summer, Fall as determined by solstice, equinox).

RESULTS

Of the patients interviewed, 31 were male, 1 female. Twenty (19 male) of the 32 (63%) patients had experienced discharges during the prior 2 years; 9 (8 male) of these 20 patients had more than one prior discharge during the 2 year time period assessed. The occurrence of discharges was confirmed by review of the medical records and defibrillator interrogation reports when available (15 of 32 respondents). Of the variables assessed for demographics purposes, the only statistically significant difference between discharge and non-discharge patients was that of PTCA status (see Table 3). None of 18 patients having discharges had had a PTCA, while 5 of 14 “no discharge” patients reported having had an angioplasty performed ($p = .019$).

Activities as triggers of discharges

Fourteen (48%) of the 29 discharges reported were triggered by physical and mental activities during daily life. Although most discharges occurred at relatively low physical activity levels, 9 of the 29 discharges (31%) were reported to have occurred at a higher physical activity level than these patients indicated was “usual”; for mental activities this percentage was 17% (5 discharges; see Table 4). Of note in inspection of the responses to the usual levels of activity questions, these groups infrequently

participate in higher levels of physical and mental activity, and there was no statistical difference between discharge and “no discharge” groups regarding baseline rates of physical and mental activities. The discharge group had an average of 2.96 (± 3.01) “high mental activities” per week, whereas the “no discharge” group had an average of 7.59 (± 9.23) “high mental activities per week ($t=-1.706$, $p=0.106$). The discharge group participated in high physical exertion activities on average only 0.07 (± 0.19) times per week, whereas the no discharge group participated in high physical exertion activities 1.21 (± 2.22) times per week ($t=-1.34$, $p=0.196$).

The Mantel-Haenszel estimate of relative risk was calculated using the reported usual activity levels for control information. Respondents were not able to reliably provide the necessary information to assess other control periods as described by Mittleman et al. such as the same time the day before or the week before (Mittleman, Maclure, & Robins, 1995). Specifically, patients remembered the immediate circumstances surrounding discharge, but rarely could they recall events any more than a few hours removed from the discharge. The estimated relative risks are summarized in Table 5. While relative risks were elevated for a number of activities, the confidence intervals include 1.00, indicating that these effects did not reach statistical significance in this small sample. The estimated relative risk (Mantel-Haenszel; RR_{MH}) for defibrillator discharge related to high physical exertion was 29.3, sexual activity was associated with an estimated relative risk of 35.4, tension or stress was associated with an estimated relative risk of 6.1. The estimated relative risk for high mental activity was 2.5, for eating the RR_{MH} was 0.68, and anger was associated with an estimated relative risk of 2.47. There were no events associated with the other 6 variables assessed (over the counter

medication use; alcohol use; smoking; illicit drug use; feeling cold/shivering; and feeling hot/sweating). An overall RR_{MH} for all physical vs. all mental activities (collapsing across categories) would be confounded by overlapping activities and was not calculated (some activities were classified as being high in intensity both on a physical level and on a mental level). Thus, while some of the Mantel-Haenszel estimates of relative risk are elevated, specifically those of high physical exertion, sex, tension and stress, anger, and high mental activity, the low number of cases prevents achieving of statistical significance in any of the specific categories, and the wide confidence intervals suggest that there is decreased confidence that the finding is entirely accurate.

A reanalysis of the activity data using a week as the unit of control time versus the two year period considered in the initial analysis yielded statistically significant results (see Table 6). The estimated relative risk for discharge associated with high levels of mental activity was 10.04 (95% confidence interval: 3.99-25.24), and the estimated relative risk for discharge associated with high levels of physical activity was 73.79 (95% confidence interval: 31.08-175.2). Tables 7 and 8 indicated the distribution of hours by level of activity and discharge grouping for high mental activity and high physical exertion. An advantage to using a week as the time unit of analysis is that it more fully mirrors the assessment of usual activities, when patients were asked, "How often in a usual week do you..." From an analysis perspective however, it eliminates consideration of hazard time during which discharges did not occur. For example, a person reported a discharge during a period of intense mental activity, and reports 2 periods of intense mental activity in a usual week. If the patient is followed over a 2 year period and has no

more discharges, that is a rate of 1 discharge per 208 episodes of intense mental activity, whereas in a week analysis, it is 1 discharge per 2 episodes.

Circadian pattern

Of 29 reported discharges, 4 (14%) of the discharges occurred in the midnight to 6:00 AM time period, 6 (21%) in the 6:00 AM to 12:00 PM period, 7 (24%) in the 12:00 PM to 6:00 PM period and 4 (14%) in the 6:00 PM to midnight period. Patients did not specify a time period for 8 (28%) discharge events for which interrogation reports were not available. These pooled data suggest higher rates of discharge between 6:00 AM and 6:00 PM, roughly equivalent to times of higher physical and mental activity during the waking day, but analysis of the 4 time periods showed that this diurnal pattern was not statistically significant ($\chi^2=1.29$, 3 *df*, $p=.73$; see Figure 5).

Seasonal pattern

Eleven (38%) of the discharges occurred in the winter season, 3 (10%) in the spring, 8 (28%) in the summer, and 2 (7%) in the fall. Patients did not specify a time of year for 5 (17%) event reports. These pooled data present a seasonal variation in ICD discharges ($\chi^2 = 9.00$, 3 *df*, $p=0.029$) with a peak in the winter and a smaller peak in the summer (see Figure 6). These discharges were not associated with time of device implant. The seasonal variation finding might be accounted for by a combination of environmental conditions such as extreme heat or cold and patients' activities in those conditions. While the environmental conditions may have been extreme, the question regarding whether the patient felt abnormally hot or cold just prior to discharge did not

yield any information to support the extreme environmental condition hypothesis. Table 9 presents the activities that occurred during or just prior to discharge categorized by season. While four of the five discharges occurring in spring and fall occurred during moderate to high physical activity, discharges occurring in winter and summer occurred with a more diverse array of activities.

DISCUSSION

Activities as triggers of discharge

In this study, nearly half of ICD discharges in CAD patients appeared to be triggered by either physical or mental activities. The estimates of relative risk suggest that high physical exertion, sexual activity, tension or stress, high mental activity and anger are associated with elevated risk for defibrillator discharge in these coronary artery disease patients, but these estimates did not reach statistically significant levels when taking into account the resulting confidence intervals. A conservative estimation of the sample size required to obtain significant confidence intervals, assuming similar rates of activities and discharges, indicated that about 80 patient interviews providing 10 discharges concurrent to or just following high mental activity would be necessary to obtain a Mantel-Haenszel risk estimate of 2.55 with a confidence interval of 1.14 to 5.70. This estimation is not a statistical power analysis- it was derived simply by extrapolating the current findings out if the current number of subjects was multiplied one and one half times, assuming similar rates of activities, discharge, and variance. It may reasonably be expected that with a larger number of subjects, and more discharge events among those

subjects, the elevated relative risks for the activities listed above would prove to be statistically significant. Such a finding would further substantiate the position that elevated physical or mental activity may increase the risk for cardiac events, in this case specifically with malignant arrhythmias leading to sudden cardiac death. Having reviewed the pathophysiology of sudden death, including the interplay of ischemia, electrical instability, and left ventricular dysfunction, it may be argued that the findings of this study support, albeit weakly, the role of mental and physical stress in acutely precipitating malignant arrhythmias.

Further discussion of the implications of the “activity as a trigger” argument has been presented by others regarding ischemia (Mittleman and Maclure, 1997). As Mittleman and Maclure point out, there are a number of questions unanswered in regard to mental and physical stress as triggers of ischemia, to include duration of effect periods of different activities, individual differences in susceptibility, the nature of the relationships between multiple activities and risk, i.e. confounding or interacting, multiplicative or additive risk modifications. As research accumulates regarding physical and mental activities as triggers of sudden cardiac death, similar questions will need to be answered. The answers may turn out to be similar in nature to the answers found regarding triggers of ischemia, or alternately, there may be some as yet undetermined factors that apply specifically to the malignant arrhythmias that lead to sudden cardiac death.

Circadian and seasonal patterns of discharge

Regarding time patterns, this pilot study provides preliminary evidence for seasonal patterns for device discharge, but does not provide evidence for a pronounced morning peak of cardiac arrhythmias and subsequent device discharges. It is suspected that a circadian pattern would have been manifest with a higher number of subjects and discharge events. Discussions regarding findings of circadian patterns of cardiac events have included various explanatory hypotheses. Postural changes related to getting out of bed in the morning, elevated levels of mental and physical activity, reduced plasma volume and endocrine changes in the body, as well as other explanations have been presented as possibly accounting for the increased number of cardiac events in the morning. A complete explanation has yet to be proffered regarding the mechanism of action in the findings of circadian patterns, but clinical cardiologists have begun to approach the issue of the implications for therapy (Muller, 1989; Singh, 1991).

Our findings regarding seasonal patterns of discharge are similar to those noted elsewhere (Fries et al., 1997), but we present as possible explanation not only the extremes of temperature associated with summer and winter months, but also the activities in which patients participate in those extreme environment conditions (Franklin, Bonzheim, Gordon, & Timmis, 1996; Kloner et al., 1998). This explanation combines consideration of both the environmental conditions and the individual's activities in accounting for seasonal variations in malignant arrhythmias.

Limitations of the study

Cautions regarding interpretation of these data include the low number of events compiled and the resulting wide confidence intervals, the lack of control for awakening time and the retrospective nature of the study. Also, even though researchers have presented that use of “usual activities” as the control period is the most efficient model (Mittleman, Maclure, & Robins, 1995), it would have been desirable to use at least one other method of control times in addition to that of “usual activities” for calculation of exposure periods. Ways to address the limitations of low number of events in future studies include increasing the number of subjects studied.

Some of the studies of arrhythmia in ICD patients mentioned earlier included arrhythmic events that did not necessarily require defibrillation therapy, whereas this study considered only events where defibrillation therapy was applied. Consideration of arrhythmic events where defibrillation does not occur, however, requires consideration of the limitations of retrospective self-reports. Almost all arrhythmic events which are terminated prior to discharge occur without the patient’s knowledge. The patient could not self-report the event, and consequently could not report the circumstances surrounding the event. The reason for not being able to use a second type of control period for comparison purposes in this study is a further illustration of some of the limitations of retrospective self-reports. While subjects were almost always able to recall the immediate circumstances surrounding a defibrillator discharge, there was considerable difficulty in recalling events and activities from the week before, or even the same time the day before the discharge event.

Beyond poor recall, there is also the risk that patients create post-hoc explanations for their discharge events, such as “I must have been really tired from the yard work,” or “I had just gotten in a heated argument,” when in actuality, the subject was minimally fatigued, or had had only a minor difference with someone. It is entirely possible that memory problems and other problems related to retrospective bias may have influenced the findings of this study. Future efforts to link activities to discharges would benefit from tracking activities before discharge events even occur, and then interviewing the patient immediately after discharge rather than up to two years later, as was done in this study. This would limit the influence of both poor recall and retrospective bias.

Another improvement in data collection would be acquiring time of awakening. This would again allow more precision regarding assessment of the role of activities, postural changes, and the physiological changes associated with awakening. The nature of the database also precluded acquisition of more detailed background medical information that might have been considered in the analysis. Assessment of psychological variables such as depressive symptomatology might have provided information regarding the possibility of an effect from seasonal affective disorder.

A last notable limitation of the study is the underlying assumption that defibrillator discharge is functionally equivalent to sudden cardiac death and that the mechanisms posited for sudden cardiac death are likely the same mechanisms for defibrillator discharge. A possible argument against this assumption follows: 1. sustained ventricular tachycardia, or even ventricular fibrillation might self-terminate prior to cardiac death, 2. there is a difference between the sustained VT and VF episodes that either do or do not lead to sudden cardiac death, and 3. this difference is more than an

issue of severity of arrhythmia. This argument states essentially that one cannot assume that defibrillator discharge events are equivalent to SCD. Such an argument, however, is not found in any of the literature cited to this point, nor has it found a prominent place in discussions of the relationship between defibrillator discharge and sudden cardiac death.

Possible mechanisms and future directions

There are a number of possible explanations for the findings regarding activities as triggers of defibrillator discharge. In accepting the assumption that defibrillator discharges are essentially equivocal with sudden cardiac death, there are similar factors for both discharges and sudden cardiac death that may be considered significant. With approximately 80 to 90% of SCD patients having coronary artery disease, and 30 to 50% of patients experiencing ischemia just prior to sudden cardiac death, the role of ischemia must be addressed. The problem of supply of and demand for oxygenated blood in cardiac tissue may be in some way involved with malignant arrhythmias. With physical and mental activities triggering ischemia, a possible explanation is that the ischemia elicits the arrhythmia or that the mechanisms triggering ischemia also trigger arrhythmia. This direct approach to accounting for sudden cardiac death by ischemia however, can only account for a fraction of events. As Bayés de Luna and colleagues (1992) point out, the severe and sustained ischemia that is sufficient to directly produce sudden cardiac death is often manifest as bradyarrhythmia. Bayés de Luna (Bayés de Luna, Guindo, et al., 1989) presented evidence, supported by others, that bradyarrhythmia is less frequently a cause of SCD than are VT and VF. The 15 interrogation reports that were available

from the subjects in this study supported their findings, in that the defibrillators were sensing VT and VF exclusively just prior to defibrillator discharge.

A further difficulty in accepting this “direct” explanation is that on the other side, 50 to 70% of sudden cardiac deaths occur without ischemia being present. What seems more plausible in explaining how activities might elicit defibrillator discharges is a vulnerability model that includes interacting factors of left ventricular dysfunction, electrical instability, and ischemia. Returning to Figure 2, physical and mental stress as well as other triggers are presented as working through a vulnerable myocardium (Bayés de Luna et al., 1992). Vulnerable myocardium (including anatomic alterations such as scar tissue or bypass grafting, depressed left ventricular function and alterations of the autonomic nervous system) may in a sense amplify or mediate the effect of the trigger, and result in the malignant ventricular arrhythmia. This model of vulnerability as a whole has not been extensively researched, although the triggers and markers have individually been shown as relevant factors in efforts to determine risk for malignant arrhythmia. To support the concept that ischemia plays an indirect role, it is noted that ischemia typically precedes the VT and VF which occurs just prior to sudden cardiac death. In sum, ischemia, left ventricular dysfunction, and electrical instability are all factors which seem to play a role in malignant ventricular arrhythmias, but rarely are any one of these factors exclusively responsible for a defibrillator discharge (and by extension, sudden cardiac death).

Regarding possible mechanisms for the seasonal effects seen in this study, the hypothesis presented by Fries et al. (1997) is that the increase in arrhythmic events during winter months is tied to thermal extremes and the stress those extremes place on the body.

Another possibility for the seasonal effects would be a corollary of that hypothesis, in which activities in those thermal extremes accentuate the stresses that thermal extremes place on the body. Franklin et al. carefully studied cardiac parameters in response to snow shoveling in the cold in 10 sedentary men and found the subjects attained heart rate responses exceeding 85% of maximal heart rate in only two minutes (Franklin et al., 1996). The oxygen consumption during snow shoveling was $5.7 (\pm 0.8)$ metabolic equivalents (METs), 39% lower than the energy expenditure of these subjects during maximal treadmill testing (9.3 ± 1.8 METs). Kloner et al. (1998) focused on diet and stress during the holiday season, noting that in their population climate was not likely to play a factor. The epidemiological approach presented by Seretakis et al. (1997) considered mortality by seasons and hypothesized that reductions in differing mortality rates by season were tied to increased climate-control use in housing. The explanation focused initially on heating prior to 1970 (changes in winter mortality), and from the 1970's to the present an increase in central- and room- air conditioning units (changes in summer mortality). Seasonal affective disorder is a possibility not assessed in our study nor the other cited research.

While the study is subject to the shortcomings noted earlier, it nonetheless provides preliminary evidence and a rationale for prospective assessment of physical and mental activities as triggers of malignant arrhythmias in ICD patients with CAD. We have recently undertaken a longitudinal study of ICD patients with CAD that will allow prospective assessment of the role of physical and mental activities as well as time-related patterns in the development of malignant arrhythmias. Another component of this recently undertaken study will provide measures with the goal of ascertaining the possible

roles of ischemia, t-wave alternans, and sympathetic and vagal influences on malignant arrhythmias from a laboratory setting. These findings can be combined with the longitudinal study to provide a more complete picture of the possible contributing factors to defibrillator discharge, and by extension, of sudden cardiac death.

TABLES

Table 1: Patient's implant etiology, indication of pace and device manufacturer/model

ID	Implant etiology	Indication of pace	Device
1	CAD	VF	MT 7217B
2	CAD	VF	MT 7217B
3	CAD	VT	MT 7219D
4	CAD, CM	VT	MT 7219B
5	CAD	VT	CPI 1715
6	SCD	VT, VF	MT 7219D
7	CAD, SCD	VT	CPI 1600
8	CAD, MI, CHF	VT	CPI 1705
9	CAD, MI, DCM	VT	MT 7217B
10	CAD	VT	MT 7219E
11	SCD, CM	VT	MT 7219B
12	CAD, MI	VT	MT 7217B
13	CAD, MI, SCD	VF	MT 7219D
14	CAD, MI	VT	MT 7219D
15	CAD, MI	VT	MT 7217B
16	CAD	VT, VF, CA	CPI 1705
17	CAD, SCD, CHF	VF, CA	MT 7219B
18	CAD	VT	CPI 1725
19	CAD	VT	CPI 1705
20	CAD, DCM	VT	MT 7219C
21	CAD	VT, FMT	MT 7219D
22	CAD	VT	MT 7219E
23	CAD	VF	CPI 1725
24	CAD, HTN	VT	MT 7217B
25	CAD, CM, SCD	VT, CA	MT 7219E
26	SCD	VT, VF	MT 7219B
27	CAD	VF	MT 7217B
28	CAD	VT, VF	MT 7217B
29	CAD	VT	MT 7219D
30	CAD, SCD, CHF	VT	MT 7217B
31	CAD, MI	VF, CA, RF	MT 7219D
32	CAD, CM	VF	CPI 1715

Implant etiology: CAD= coronary artery disease; MI= previous myocardial infarction; SCD= sudden cardiac death; CHF = congestive heart failure; HTN= hypertension; CM= cardiomyopathy, DCM= dilated cardiomyopathy; **Indication of pace:** VT= ventricular tachycardia; VF= ventricular fibrillation; CA= cardiac arrest; FMT= failed medical therapy; RF= high risk factors; **Manufacturers:** CPI= Cardiac Pacemakers, Inc; MT= Medtronic

Table 2: Patient Demographics and Clinical Characteristics

	N	Mean (Sd)	Range
Age	30	67.07 (9.61)	40-81
LVEF	13	35.08%(12.87)	14-50 %
BMI	32	27.29 (6.07)	17-44
History of	N	Percent Positive	
PTCA	5/32	16%	
CABG	12/32	38%	
Previous MI	29/32	91%	
Diabetes	9/32	28%	

N= number of subjects; Sd= standard deviation; LVEF= Left ventricular ejection fraction; BMI= Body-Mass Index; PTCA= percutaneous transluminal coronary angioplasty; CABG= coronary artery bypass graft; MI= myocardial infarction.

Table 3: Patient Demographics and Clinical Characteristics by Discharge Status

	Discharge	No Discharge
	Mean (Sd)	Mean (Sd)
Age	67.06 (10.83)	67.07 (8.4)
LVEF	32.33 (15.21)	37.43 (11.15)
BMI	26.62 (4.42)	28.16 (7.80)
	Proportion positive (%)	Proportion positive (%)
Diabetes	4/18 (22)	5/14 (36)
CABG	7/18 (39)	5/14 (36)
PTCA	0/18 (0)	5/14 (36) *
Previous MI	18/18 (100)	11/14 (79)

*p= .019; Sd= standard deviation; LVEF= Left ventricular ejection fraction; BMI= Body-Mass Index; PTCA= percutaneous transluminal coronary angioplasty; CABG= coronary artery bypass graft; MI= myocardial infarction.

Table 4: Triggers of 29 defibrillator discharges during activities of daily life retrospectively identified in 20 pts with ICD's and coronary artery disease.

<u>Activity</u>	<u>N</u>	<u>%</u>
during sleep	5	17.2
reclining	3	10.3
low physical	7	24.1
high physical	8	27.6
Sexual activity	1	3.4
high mental	5	17.2

N= number of discharges preceded by each type of activity

%= percent of 29 discharges in each activity

Table 5: Mantel-Haenszel estimates of relative risk by activity.

<u>Activity</u>	<u># of cases</u>	<u>RR_{MH}</u>	<u>Var [ln(RR_{MH})]</u>	<u>χ</u>	<u>C.I.</u>
Anger	2	2.47	40.28	0.32	0.01-684
Mental Activity	4	2.55	19.20	0.91	0.34-19.03
Eating	2	0.68	13.74	0.54	0.17-2.76
Physical Exertion	5	29.29	15.02	1.29	0.17-4950
Tense/ Stressed	4	6.09	13.66	1.08	0.23-160
Sex	1	34.93	33.57	0.17	0.00- ∞
Smoking	0*
Cold/ Shivering	0*
Hot/ Sweating	0*
Cough Med	0*
Drugs	0*

*No risks calculated as there are no cases. # of cases= number of discharge events occurring within 1 hour of the noted activity. RR_{MH}= Mantel Haenszel estimator of relative risk. Var[ln(RR_{MH})] = variance of the log of the Mantel Haenszel estimator. χ = Chi. C.I.= confidence interval.

Table 6: Estimates of relative risk for discharge with high physical and mental activity using week as unit of analysis

<u>Activity</u>	<u>Risk Estimate</u>	<u>Confidence Interval</u>
High mental activity	10.04	3.99-25.24
High physical activity	73.79	31.08-175.2

Table 7: Distribution of mental activity status hours by discharge group-week as unit of analysis

High Mental Activity	Not high mental activity	High mental activity
No discharge group	5201	148
Discharge group	21	6

Table 8: Distribution of physical exertion status hours by discharge group-week as unit of analysis

High Physical Exertion	Not high physical exertion	High physical exertion
No discharge group	5313	36
Discharge group	18	9

Table 9: Activities associated with discharges categorized by season.

Season	#Discharges	Activities
Winter	11	High Mental Activity, Sleep (2), High Physical Activity (3), Talking on phone, Eating/standing, Anger, Getting out of chair(posture change), Standing
Spring	3	Moderate Physical Activity, Rest, High Physical Activity
Summer	8	Rest, Sex, Anger (2), Defecation, High Physical Activity,
Fall	2	High Physical Activity (2)

FIGURES

Figure 1: Risk markers of sudden death in post-myocardial infarction patients
(Bayés de Luna et al., 1992)

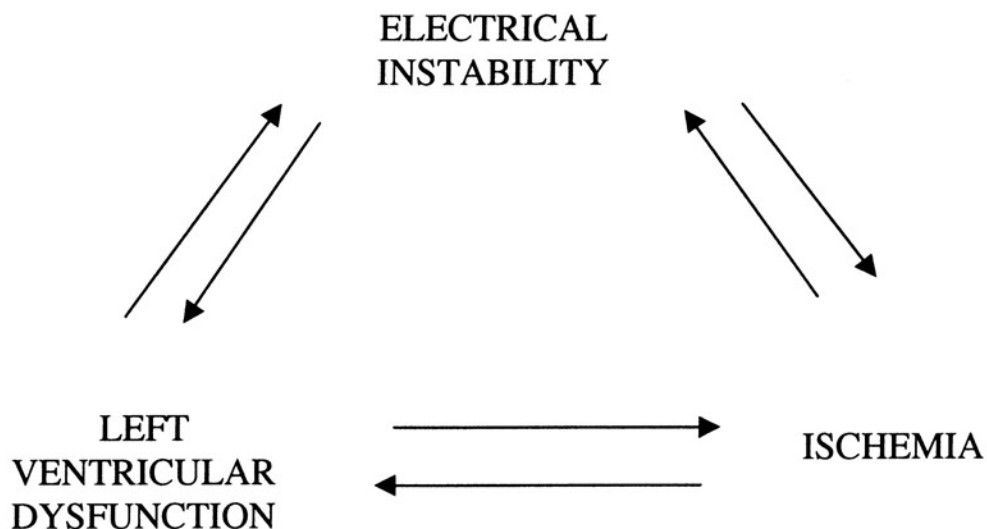


Figure 2: Triggers and markers interacting to lead to malignant ventricular arrhythmias and sudden cardiac death (Bayés de Luna et al., 1992).

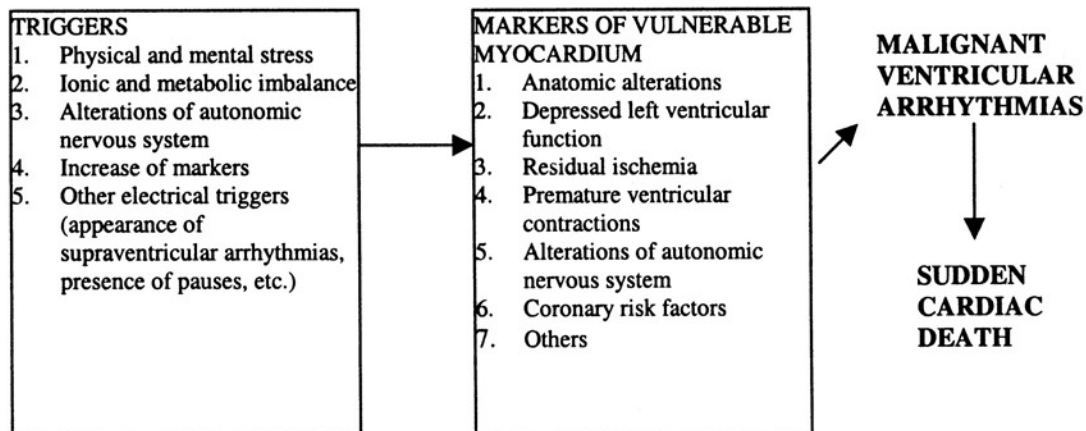


Figure 3: Circadian pattern of nonfatal myocardial infarction
(n = 66,635; Cohen, Rohtla, Lavery, Muller, & Mittleman, 1997)

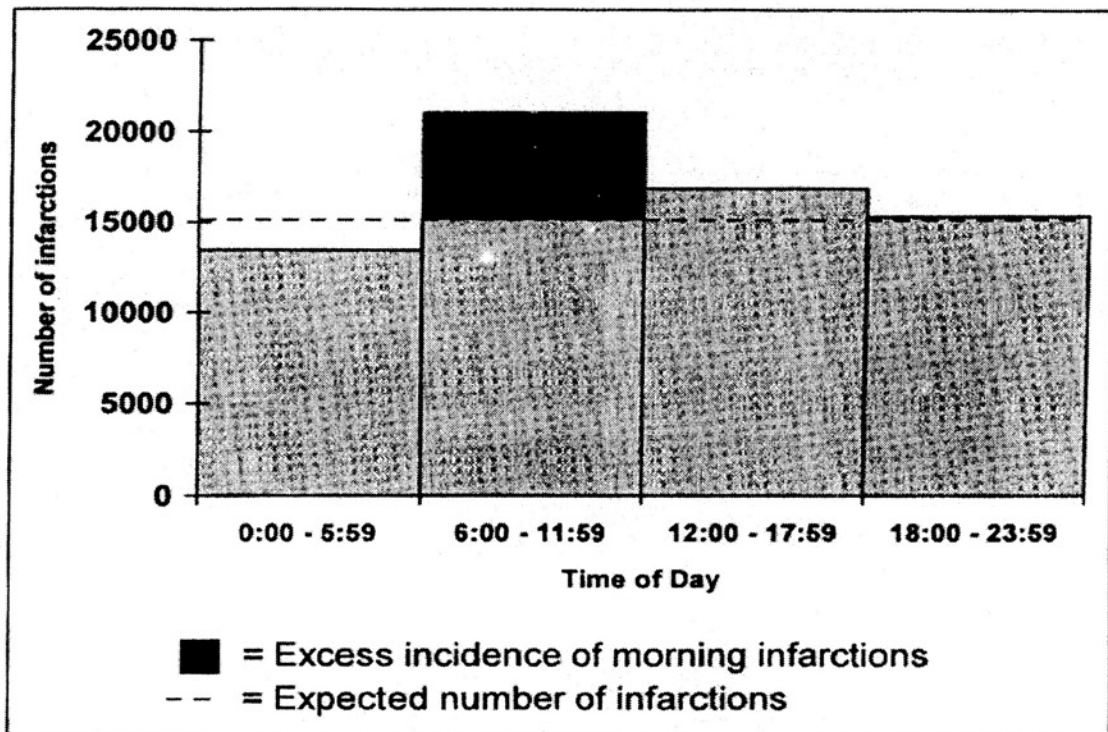


Figure 4: Circadian pattern of sudden cardiac death
(n = 19,390; Cohen, Rohtla, Lavery, Muller, & Mittleman, 1997)

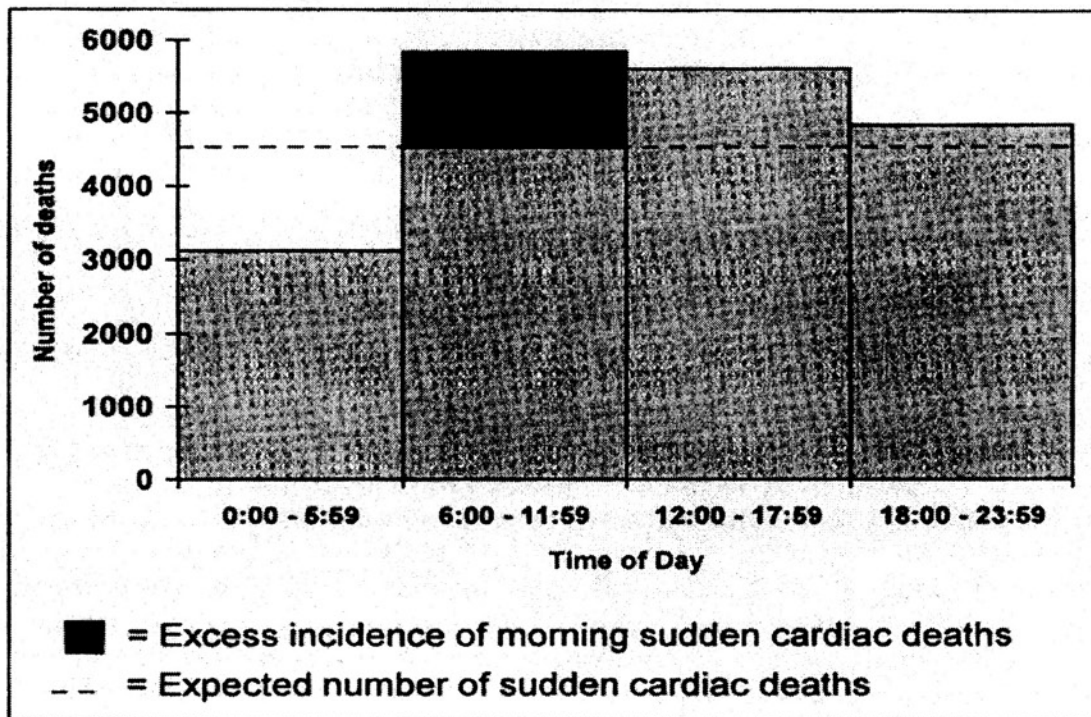


Figure 5: Circadian pattern of ICD discharge.

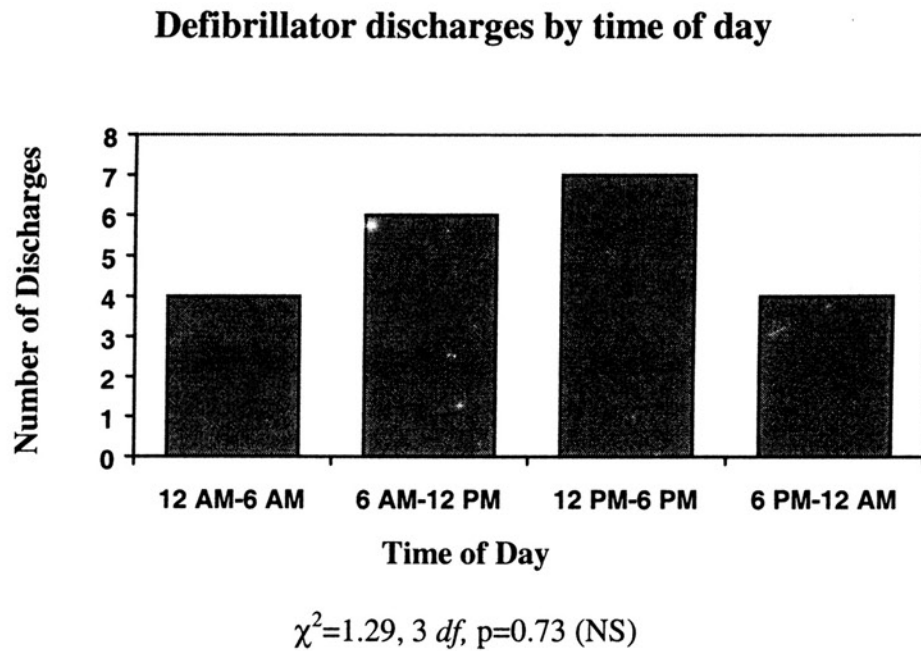
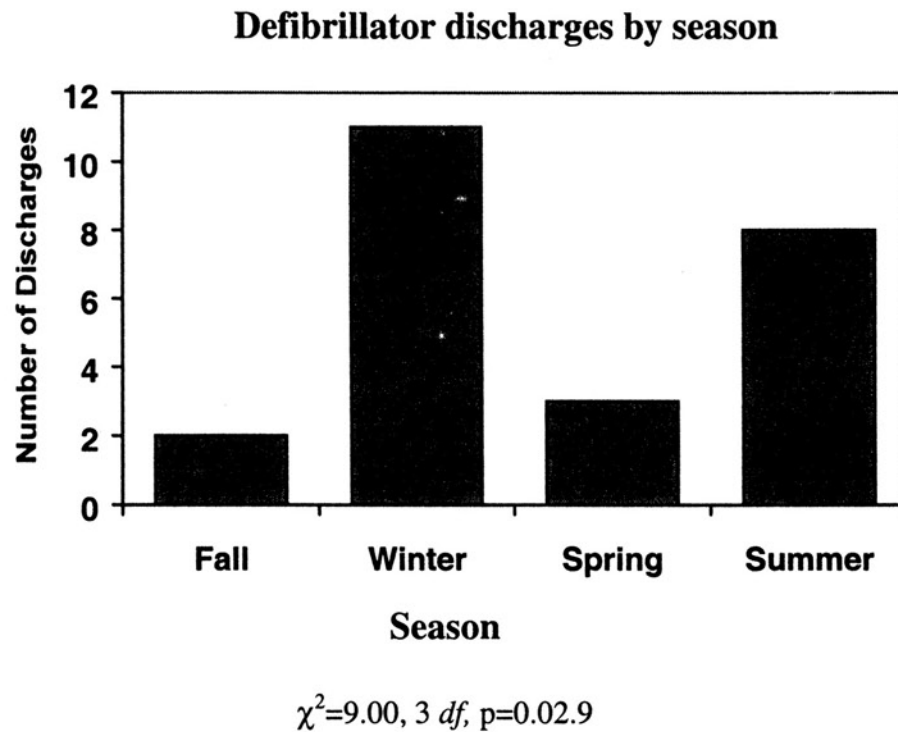


Figure 6: Seasonal pattern of ICD discharge.



APPENDIX A

The retrospective interview.

Event Questionnaire (pilot information) RO7233
 Questionnaire draft date: 12 June, 1998
 file:icdques4.doc

Pt. ID# _____ Date: ____/____/____ Time interview conducted: _____

(Introduction)--Hello, Mr./Mrs. _____, my name is _____, I'm a research assistant working with the Division of Cardiology at the Veterans Affairs Medical Center in Washington D.C.

How you have been doing recently?

We are investigating factors possibly contributing to implantable cardioverter defibrillator discharge. We would like to conduct an interview with you concerning your health status, your usual activities, and circumstances surrounding recent device discharges you might have had. This will take about 30 minutes to conduct. Confidentiality of the information obtained in this interview will be strictly upheld.

May I conduct this interview with you? Yes _____ No _____

If no, reason: _____

Please give your best answer to each question, or indicate if you do not know or cannot remember.

Have you ever had any discharges from your device? yes no

Current clinical status/ Medical history section

The first few questions are on your current health situation and what a "usual week" entails.

Height _____ Weight _____

Cardiovascular disease (CVA, peripheral) yes no
 specify _____

Lung disease yes no
 specify _____

History of myocardial infarction yes no
 If yes, date _____

History of congestive heart failure requiring treatment yes no

History of hypertension yes no
 Current therapy:
 Medication _____ (1)
 Diet _____ (2)
 Both _____ (3)
 Neither _____ (4)

History of diabetes yes no
 Current therapy:
 Oral medication _____ (1)
 Insulin _____ (2)
 Both _____ (3)
 Neither _____ (4)

PTCA yes no

CABG yes no

Other cardiovascular procedures yes no

Current medications and period they have been taken

1. _____ (how long?) _____

2. _____ (how long?) _____

3. _____ (how long?) _____

4. _____ (how long?) _____

5. _____ (how long?) _____

6. _____ (how long?) _____

Section on “usual activities”

How often in a usual week do you participate in the following activities?	Usual Frequency	Usual duration	Frequency in past week
Extreme or peak exertion (e.g. sprinting, fast running, fast jogging, or jogging uphill, pushing and pulling with all your might, usually extreme work)			
Heavy exertion , with gasping; much sweating (e.g. running, fast jogging, pushing a car stuck in snow, changing tires, shoveling heavy or deep snow, competitive basketball, putting down wall-to-wall carpet, ladder or stair climbing with a 50 lb. load)			
Vigorous exertion , with panting; overheating (e.g. slow jogging, tennis, swimming, cross-country skiing, shoveling snow, fast biking, mowing with a push mower, heavy gardening, climbing up/down a ladder, softball, laying bricks, hurried heavy restaurant work)			
Moderate exertion , with deep breathing (e.g. normal walking, golfing on foot, slow biking, downhill skiing, raking leaves, cleaning windows, interior painting, slow dancing, light restaurant work)			
Light exertion , with normal breathing (e.g. mopping, slow walking, bowling, sweeping, golfing with a cart, gardening with power tools)			
Sexual intercourse			
How often in a usual week do you experience the following?	Usual frequency	Usual duration	Frequency in past week
Enraged (you’ve lost control, throw objects, hurting yourself or others)			
Furious (almost out of control, very angry, pounding table, slamming door)			
Very Angry (body tense, clenching fists or teeth)			
Moderately angry (so hassled it shows in your voice)			
Mildly angry , irritated and hassled (but it does not show)			
Extremely tense (fear or panic, periods of shaking, dizziness, or intense distress)			
Very tense (worries interfering with sleep or concentration)			
Moderately tense (restless, keyed up, upset)			
Mildly tense (worried or preoccupied)			

How often in a usual week do you shiver or have goose bumps?			
How often in a usual week are so hot that you are sweating heavily or feeling overheated?			
How often in a usual week do you drink beer, wine, or liquor? How much do you drink? _____ glasses of beer _____ glasses of wine _____ shots of liquor/mixed drinks			
How often in a usual week do you drink caffeinated beverages (coffee, tea, cola)? How much do you drink? _____ cups of coffee _____ cups of tea _____ glasses of cola			
How many cigarettes do you smoke in a usual week?		(How long to smoke a cig.?)	Number cigs past week
How many meals do you eat in a usual day?			
How often do you use cough, cold, or allergy medicines or diet pills? Name of products: _____			
How often in an average week do you participate in the following levels of activity?	Frequency	Usual duration	# times in past week
Intense mental activity (high levels of concentration, anger, or anxiety)			
Elevated mental activity (driving, moderate levels of anger or anxiety)			
Moderate mental activity (talking, clerical work, thinking, shopping)			
Light mental activity (reading, watching television, listening to the radio)			
Very light mental activity (sleep, rest)			

Discharge section (up to 2 episodes)

1. How many discharges have you had since implantation of the device? _____
 How many discharges has the device given in the past 2 years? _____

Most recent device discharge

2. Date and time of most recent discharge _____/_____/_____ :_____ AM PM
3. Were any of your usual medications missed in the 24 hours prior to the discharge for any reason?

Yes No

If yes, which? _____
 why? _____

4. Were any changes made in your medications in the week prior to the discharge? Yes No

If yes, what? _____

5. Were you having any symptoms before the device discharge? Yes No

If yes, what were they?

How long before the device discharge?
 (e.g. 5 mins before, 2 hours before)

___ headache
 ___ chest pain, discomfort, angina
 ___ hunger
 ___ dizziness
 ___ nausea or vomiting
 ___ sore joints
 ___ palpitations
 ___ shortness of breath
 ___ other: _____

6. What were you doing when the discharge occurred?

___ going to sleep	___ sleep	___ rest
___ washing/dressing	___ urination/defecation	___ driving/passenger
___ eating/drinking (non-alcohol)		___ smoking
___ caffeine	___ alcohol	___ walking/shopping
___ stair climbing	___ sexual activity	___ other: _____

7. What time did you wake up on the day of the device discharge? _____:_____ AM PM

In this next section of the questionnaire you will be asked to indicate the last time you engaged in a particular level of exertion, activity, or experienced a particular mood or emotion prior to your **most recent device discharge**. (If the patient has not done that particular activity, or experienced that emotion since the device was implanted, write N/A--not applicable-- in the appropriate column.)

To help you remember the answers, what was the time and date of your **most recent device discharge**?

Time: _____ **AM PM** **Date:** _____

When was the last time before device discharge that you engaged in:	Best guess of time interval:	If patient knows exact time and date:
Extreme or peak exertion (e.g. sprinting, fast running, fast jogging, or jogging uphill, pushing and pulling with all your might, usually extreme work)		time: date:
Heavy exertion, with gasping; much sweating (e.g. running, fast jogging, pushing a car stuck in snow, changing tires, shoveling heavy or deep snow, competitive basketball, putting down wall-to-wall carpet, ladder or stair climbing with a 50 lb. load)		
Vigorous exertion, with panting; overheating (e.g. slow jogging, tennis, swimming, cross-country skiing, shoveling snow, fast biking, mowing with a push mower, heavy gardening, climbing up/down a ladder, softball, laying bricks, hurried heavy restaurant work)		
Moderate exertion, with deep breathing (e.g. normal walking, golfing on foot, slow biking, downhill skiing, raking leaves, cleaning windows, interior painting, slow dancing, light restaurant work)		
Light exertion, with normal breathing (e.g. mopping, slow walking, bowling, sweeping, golfing with a cart, gardening with power tools)		
Sexual intercourse		
When was the last time before device discharge that you felt:	Best guess of time interval:	If patient knows exact time and date:
Enraged (you've lost control, throw objects, hurting yourself or others)		
Furious (almost out of control, very angry, pounding table, slamming door)		
Very Angry (body tense, clenching fists or teeth)		
Moderately angry (so hassled it shows in your voice)		
Mildly angry, irritated and hassled (but it does not show)		
Extremely tense (fear or panic, periods of shaking, dizziness, or intense distress)		
Very tense (worries interfering with sleep or concentration)		
Moderately tense (restless, keyed up, upset)		

Mildly tense (worried or preoccupied)		
When was the last time before device discharge that you were shivering or had goose bumps?		
When was the last time you were so hot that you were sweating heavily or feeling overheated?		
When was the last time you drank beer, wine, or liquor? How much did you drink? _____ glasses of beer _____ glasses of wine _____ shots of liquor/mixed drinks		
When was the last time you drank caffeinated beverages (coffee, tea, cola)? How much did you drink? _____ cups of coffee _____ cups of tea _____ glasses of cola		
When was the last time you smoked a cigarette?		
When was the last time you ate a meal? Was it so large that you felt bloated? yes no		
When was the last time you used cough, cold, or allergy medicines or diet pills? Name of products: _____		
When was the last time before discharge that you engaged in:	Best guess of time interval:	If patient knows exact time and date:
Intense mental activity (high levels of concentration, anger, or anxiety)		
Elevated mental activity (driving, moderate levels of anger or anxiety)		
Moderate mental activity (talking, clerical work, thinking, shopping)		
Light mental activity (reading, watching television, listening to the radio)		
Very light mental activity (sleep, rest)		

Section on Second-most recent device discharge

1. Date and time of second-most recent discharge ____/____/____ :____ AM PM

2. Were any of your usual medications missed in the 24 hours prior to the discharge for any reason?
Yes No

If yes, which? _____
why? _____

3. Were any changes made in your medications in the week prior to the discharge? Yes No

If yes, what? _____

4. Were you having any symptoms before the device discharge? Yes No

If yes, what were they?

How long before the device discharge?
(e.g. 5 mins before, 2 hours before)

____ headache
____ chest pain, discomfort, angina
____ hunger
____ dizziness
____ nausea or vomiting
____ sore joints
____ palpitations
____ shortness of breath
____ other: _____

5. What were you doing when the discharge occurred?

____ going to sleep	____ sleep	____ rest
____ washing/dressing	____ urination/defecation	____ driving/passenger
____ eating/drinking (non-alcohol)		____ smoking
____ caffeine	____ alcohol	____ walking/shopping
____ stair climbing	____ sexual activity	____ other: _____

6. What time did you wake up on the day of the device discharge? ____:____ AM PM

In this section of the questionnaire you will be asked to indicate the last time you engaged in a particular level of exertion, activity, or experienced a particular mood or emotion prior to your second most recent device discharge. (If the patient has not done that particular activity, or experienced that emotion since the device was implanted, write N/A--not applicable-- in the appropriate column.)

To help you remember the answers, what was the time and date of your **second most recent device discharge?**

Time: _____ **AM PM** **Date:** _____

When was the last time before device discharge that you engaged in:	Best guess of time interval:	If patient knows exact time and date:
Extreme or peak exertion (e.g. sprinting, fast running, fast jogging, or jogging uphill, pushing and pulling with all your might, usually extreme work)		time: date:
Heavy exertion, with gasping; much sweating (e.g. running, fast jogging, pushing a car stuck in snow, changing tires, shoveling heavy or deep snow, competitive basketball, putting down wall-to-wall carpet, ladder or stair climbing with a 50 lb. load)		
Vigorous exertion, with panting; overheating (e.g. slow jogging, tennis, swimming, cross-country skiing, shoveling snow, fast biking, mowing with a push mower, heavy gardening, climbing up/down a ladder, softball, laying bricks, hurried heavy restaurant work)		
Moderate exertion, with deep breathing (e.g. normal walking, golfing on foot, slow biking, downhill skiing, raking leaves, cleaning windows, interior painting, slow dancing, light restaurant work)		
Light exertion, with normal breathing (e.g. mopping, slow walking, bowling, sweeping, golfing with a cart, gardening with power tools)		
Sexual intercourse		
When was the last time before device discharge that you felt:	Best guess of time interval:	If patient knows exact time and date:
Enraged (you've lost control, throw objects, hurting yourself or others)		
Furious (almost out of control, very angry, pounding table, slamming door)		
Very Angry (body tense, clenching fists or teeth)		
Moderately angry (so hassled it shows in your voice)		
Mildly angry, irritated and hassled (but it does not show)		
Extremely tense (fear or panic, periods of shaking, dizziness, or intense distress)		
Very tense (worries interfering with sleep or concentration)		
Moderately tense (restless, keyed up, upset)		
Mildly tense (worried or preoccupied)		

When was the last time before device discharge that you were shivering or had goose bumps?		
When was the last time you were so hot that you were sweating heavily or feeling overheated?		
When was the last time you drank beer, wine, or liquor? How much did you drink? _____ glasses of beer _____ glasses of wine _____ shots of liquor/mixed drinks		
When was the last time you drank caffeinated beverages (coffee, tea, cola)? How much did you drink? _____ cups of coffee _____ cups of tea _____ glasses of cola		
When was the last time you smoked a cigarette?		
When was the last time you ate a meal? Was it so large that you felt bloated? yes no		
When was the last time you used cough, cold, or allergy medicines or diet pills? Name of products: _____		
When was the last time before discharge that you engaged in:	Best guess of time interval:	If patient knows exact time and date:
Intense mental activity (high levels of concentration, anger, or anxiety)		
Elevated mental activity (driving, moderate levels of anger or anxiety)		
Moderate mental activity (talking, clerical work, thinking, shopping)		
Light mental activity (reading, watching television, listening to the radio)		
Very light mental activity (sleep, rest)		

Thank you for your responses to the questionnaire. This information will help in our efforts to more fully understand the physical and mental factors contributing to ICD discharges.

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